Wilmer Eye Institute
Johns Hopkins Medicine

Similar risk of kidney failure among patients with blinding diseases who receive ranibizumab, aflibercept, and bevacizumab: an OHDSI Network Study

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6/25/2024

SOS Challenge Weekly Tutorial Schedule
2023

Date	Times	Topic
Mar. 28	11 am / 7 pm ET	SOS Week 1 Tutorial: Initiating A Network Study
Apr. 4	11 am / 7 pm ET	SOS Week 2 Tutorial: Data Diagnostics
Apr. 11	11 am / 7 pm ET	SOS Week 3 Tutorial: Phenotype Development
Apr. 18	11 am / 7 pm ET	SOS Week 4 Tutorial: Phenotype Evaluation
Apr. 25	11 am / 7 pm ET	SOS Week 5 Tutorial: Creating Analysis Specifications
May 2	11 am / 7 pm ET	SOS Week 6 Tutorial: Network Execution
May 9	11 am / 7 pm ET	SOS Week 7 Tutorial: Study Diagnostics
May 16	11 am / 7 pm ET	SOS Week 8 Tutorial: Evidence Synthesis
May 23	11 am / 7 pm ET	SOS Week 9 Tutorial: Interpreting The Results

Background: anti-VEGF medications

- Systemic administration of anti-VEGF agents have known **adverse kidney side effects**
  - Acute kidney injury
  - Proteinuria
  - Hypertension
  - Vascular clotting events
  - Glomerular disease
  - Risk factors for: kidney failure (need for renal replacement therapy with dialysis or kidney transplant, aka end stage kidney disease or end stage renal disease)

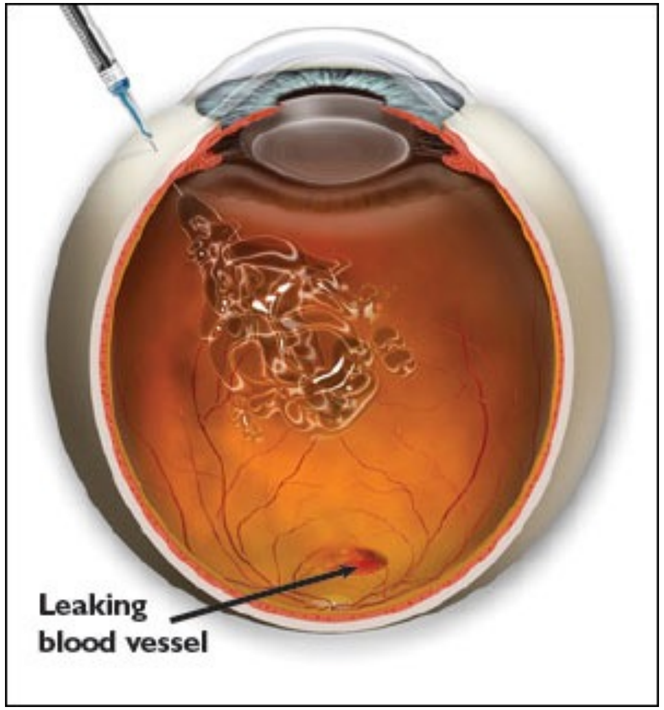
Hanna RM, Barsoum M, Arman F, Selamet U, Hasnain H, Kurtz I. Nephrotoxicity Induced by Intravitreal Vascular Endothelial Growth Factor (VEGF) inhibitors: Emerging Evidence. *Kidney Int*. 2019;96(3):572-580. doi:10.1016/j.kint.2019.02.042

Gurevich F, Perazella MA. Renal Effects of Anti-angiogenesis Therapy: Update for the Internist. *Am J Medicine*. 2009;122(4):322-328. doi:10.1016/j.amjmed.2008.11.025

Izzedine H, Escudier B, Lhomme C, et al. Kidney Diseases Associated With Anti-Vascular Endothelial Growth Factor (VEGF). *Medicine*. 2014;93(24):333-339. doi:10.1097/md.0000000000000207

Brandes, A. A., Bartolotti, M., Tosoni, A., Poggi, R. & Franceschi, E. Practical Management of Bevacizumab-Related Toxicities in Glioblastoma. *Oncol* **20**, 166–175 (2015).

Intravitreal Anti-VEGF and Systemic Absorption



Drug	Size	Systemic Elimination (half-life)
Ranibizumab	48 kDa	2 hours
Aflibercept	115 kDa	5-6 days
Bevacizumab	149 kDa	20 days

Detectable/elevated serum drug levels
Decreased plasma concentrations of free-VEGF

Bevacizumab > aflibercept >> ranibizumab

Question: Is there evidence for preferentially choosing ranibizumab to lower the risk of kidney failure?

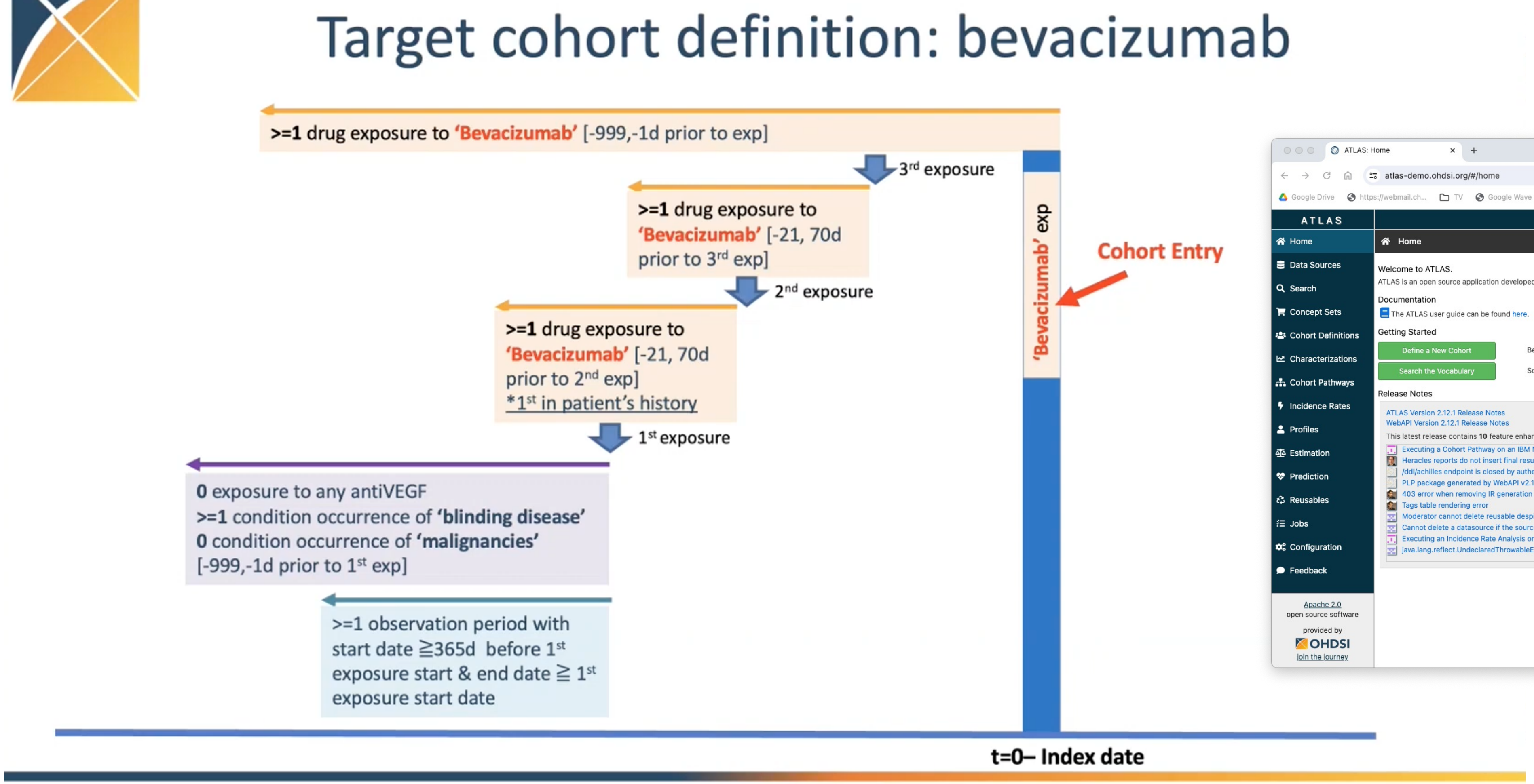
https://www.randeye.com/intravitreal-injection/
Avery RL, Castellarin AA, Steinle NC, et al. SYSTEMIC PHARMACOKINETICS AND PHARMACODYNAMICS OF INTRAVITREAL AFLIBERCEPT, BEVACIZUMAB, AND RANIBIZUMAB. *Retin*. 2017;37(10):1847-1858. doi:10.1097/iae.0000000000001493
https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/125085s0169lbl.pdf

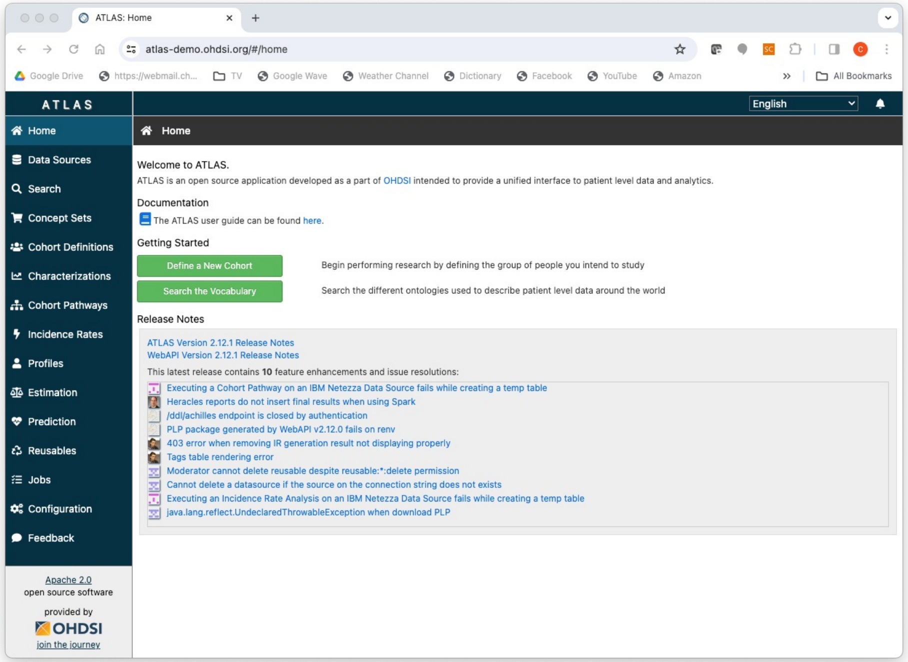
Pilot Study (OHDSI SOS Challenge): Intravitreal anti-VEGF and Kidney Failure

- Is the risk of kidney failure associated with intravitreal anti-VEGF exposure in patients with blinding diseases (DR/DME, AMD, VO) different among patients who receive ranibizumab, aflibercept, and bevacizumab?

Hypothesis: in pairwise comparisons, lower risk of kidney failure in patients with blinding diseases who are exposed to ranibizumab, as compared to aflibercept or bevacizumab

OHDSI Tools: Atlas





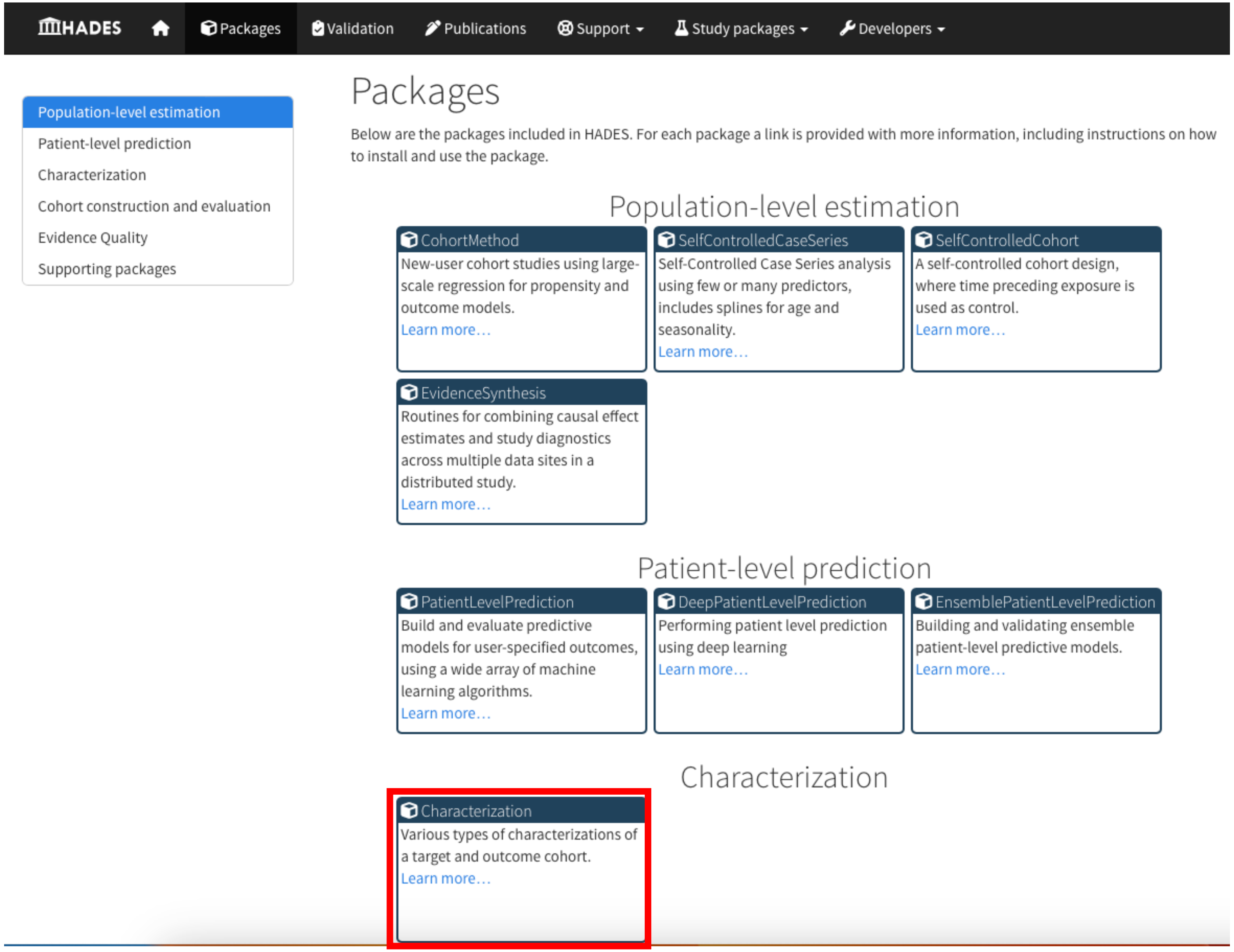
New users of anti-VEGF (3 monthly loading doses)
DR/DME, AMD, VO
≥1 year observation prior observation
Exclude systemic malignancies

Atlas: publicly available, web-based tool

OHDSI Tools: Strategus pipeline, HADES packages

Analysis #1:

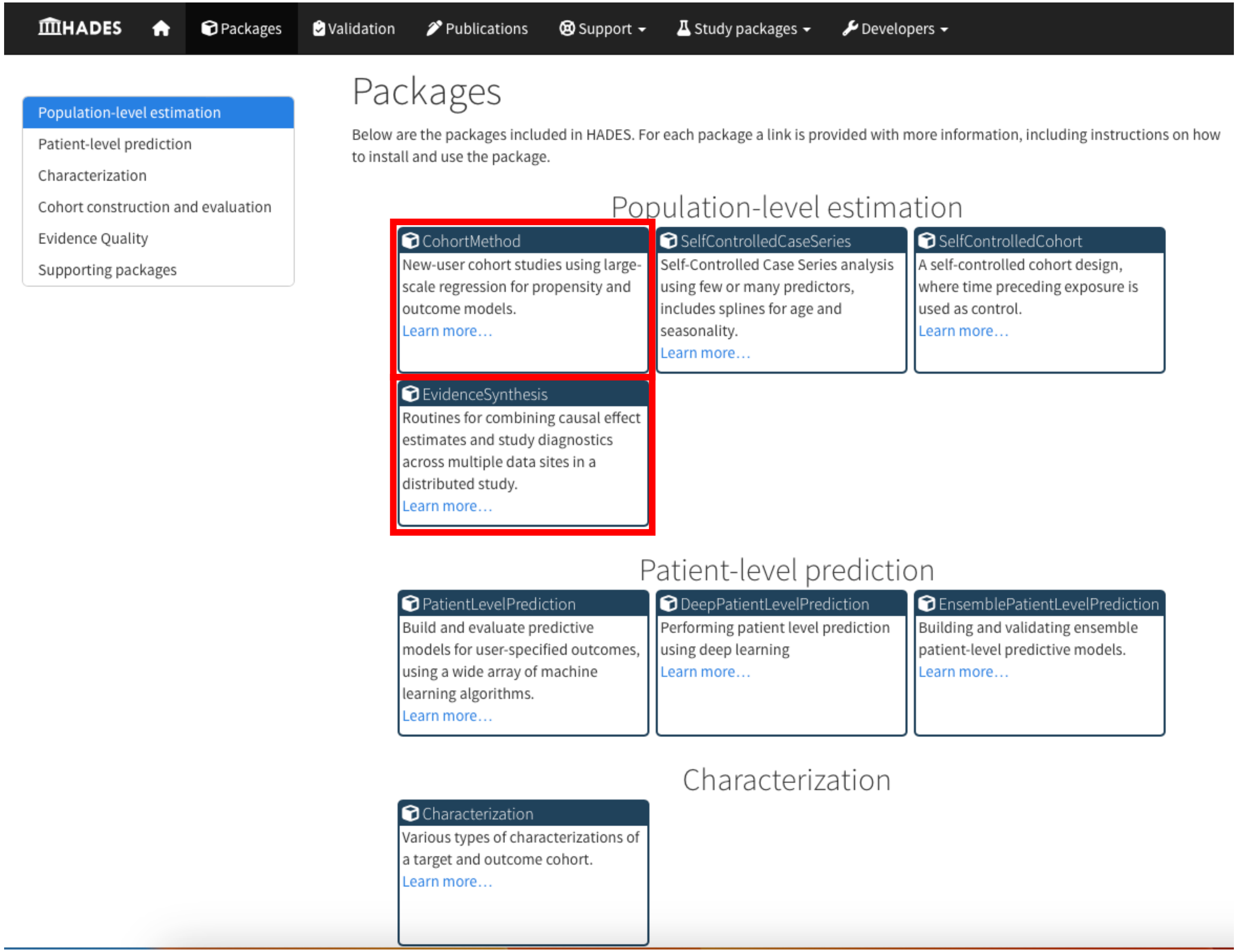
- Incidence rate of kidney failure while on treatment with anti-VEGF



OHDSI Tools: Strategus pipeline, HADES packages

<u>Analysis #2</u>:

- Large-scale propensity score method to match patients in each comparison group using 1:1 propensity score matching
- Cox proportional hazards models to estimate risk of kidney failure while on treatment
- Random effects meta-analysis was performed to combine per site hazard ratio estimates into a single network-wide estimate



Anti-VEGF OHDSI Study: Process

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Collectively: 485 million patients

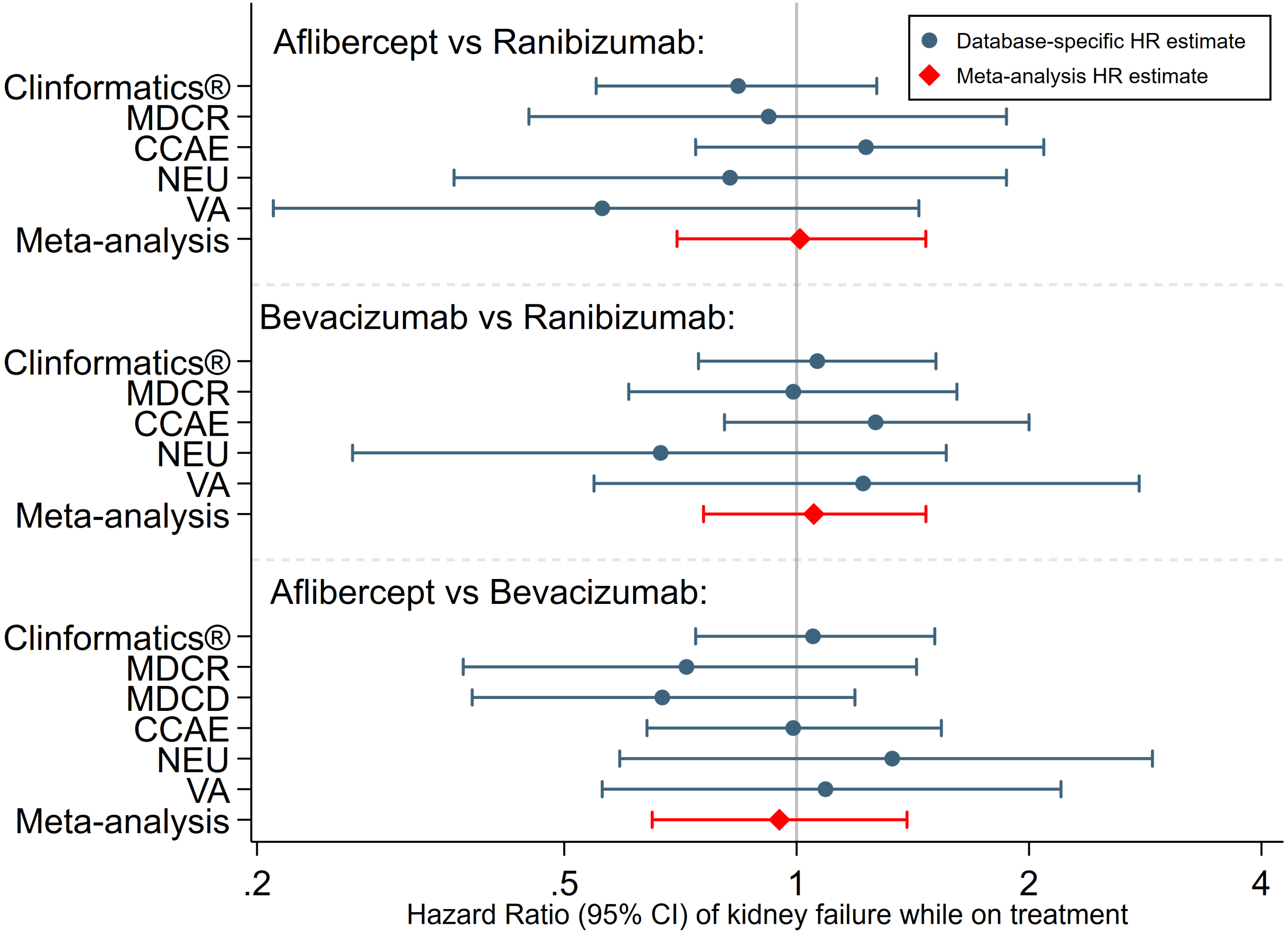
Administrative Claims Databases
IBM Health MarketScan Medicare Supplemental and Coordination of Benefits Database (MDCR)
IBM Health MarketScan Commercial Claims and Encounters Database (CCAE)
IBM Health MarketScan Multi-State Medicaid Database (MDCD)
Optum's de-identified Clinformatics® Data Mart Database - Socio-economic Status (SES)
Japan Medical Data Center (JMDC)
IQVIA PharMetrics® Plus for Academics Database (NEU)

Electronic Health Record Databases
Optum® de-identified Electronic Health Record data set (Optum EHR)
Johns Hopkins Medical Enterprise (JHME)
Department of Veterans Affairs (VA)
Columbia University Medical Center (CUMC)
Stanford University (STARR)
University of Southern California (USC)

Anti-VEGF OHDSI Study: Results

- 6.1 million patients with blinding diseases (DR/DME, AMD, VO)
  - 240,247 new users of monthly anti-VEGF
    - 37,189 received ranibizumab
    - 39,447 aflibercept
    - 163,611 bevacizumab
  - 1209 kidney failure outcomes
- Age-sex standardized incidence proportion of kidney failure: **680 per 100,000** persons
  - [US Renal Data System: age-sex standardized incidence proportion of 36.3 per 100,000 persons in 2020]

Anti-VEGF OHDSI Study: Results



Conclusions

- No difference in the risk of kidney failure among patients who receive ranibizumab, aflibercept, bevacizumab
- Ophthalmologists are free to choose between intravitreal anti-VEGF agents

Conclusions

- Speed and scale of observational health research when there is a CDM, well-established distributed data network, open-source tooling
  - Analysis in 9 weeks
  - Project initiation to publication 1 year
- Great value and potential for distributed data network studies in ophthalmology

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Similar Risk of Kidney Failure among Patients with Blinding Diseases Who Receive Ranibizumab, Aflibercept, and Bevacizumab

An Observational Health Data Sciences and Informatics Network Study

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